

Correspondence

Reply

To the Editor:

We thank Theoharides and Leeman¹ for their positive comments on our review,² which focused on recent developments in the understanding of human mast cell biology. It is gratifying to see this large number of recent scientific reports from which we selected only a portion of many interesting and novel experimental approaches and observations. The understanding of mast cell biology has lagged somewhat behind studies on other effector cells because mast cells do not normally occur in blood, there is no human condition characterized by the absence of mast cells in all tissues, and there is no pharmacologic therapy that specifically and only silences mast cell function. However, the relatively recent availability of human mast cell lines, including LAD2 cells developed in our laboratory,^{3,4} along with improved techniques to more easily culture human mast cells⁵ and to more easily obtain mast cells from human tissues such as skin and marrow,^{6,7} have facilitated research into this interesting cell.

In the 2 more recent articles cited by Theoharides and Leeman, they reported that IL-33 regulated IL-31 gene expression in the LAD2 cell line stimulated with substance P (SP)⁸ and that combined treatment of SP and IL-33 markedly enhanced TNF synthesis and secretion from LAD2 cells and mast cells cultured from human umbilical cord.⁹ The authors also suggest a physical interaction between the receptors for SP (neurokinin 1 receptor; NK1) and IL-33.⁹ It is important, however, that such experiments are taken to the next level. For example, mast cells may be obtained from human skin. Such cells may respond very differently from cell lines and mast cells differentiated *in vitro* from progenitors due to epigenetic changes and in the context of *in vivo* tissue differentiation. And ideally, it would be even more convincing to show within tissues similar outcomes in inflammation where SP and IL-33 are produced in the same inflammatory reaction. It might also be possible to use mouse (eg, mice genetically deficient in NK1 or in the receptor for IL-33) and humanized mouse models as we review in our article.² These approaches might help

to assess the physiopathological implications of the interactions between SP and IL-33.

Nevertheless, such *in vitro* modeling is important in that it shows us possibilities and, in this case, potential important interactions between human mast cells, SP, and IL-33.

Ana Olivera, PhD

Dean D. Metcalfe, MD

From the Mast Cell Biology Section, Laboratory of Allergic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md. E-mail: Ana.olivera@nih.gov.

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